Motoyama JP-S57-142911 Application Pub

(19) Japanese Patent Office (JP)
(12) Unexamined Patent Publication Bulletin (A)

(11) Patent Application Laid-Open Disclosure Number: S57-142911

(51) Int. Cl.[3]	Identification Code	JPO File No.
A 61 K 9/14		7057-4C
//A 61 K 31/12		

(43) Disclosure Date: Sept. 3, 1982
No. of Inventions: 2
Examination Request Status: Not yet requested
(6 pages total)

(54) Absorption Improvement Formulation

(21) Patent Application No.: Patent Filing No. S56-27663
(22) Filing Date: February 28, 1981

(72) Inventor: Shimesu MOTOYAMA
c/o Furointo Sangyo, KK
14-2 Takadanobaba 2-chome, Shinjuku-ku, Tokyo
(72) Inventor: Satoru SATO
c/o Furointo Sangyo, KK
14-2 Takadanobaba 2-chome, Shinjuku-ku, Tokyo
(72) Inventor: Seiichi UMEDA
c/o Furointo Sangyo, KK
14-2 Takadanobaba 2-chome, Shinjuku-ku, Tokyo
(72) Inventor: Hirotsune YASUMI
c/o Furointo Sangyo, KK
14-2 Takadanobaba 2-chome, Shinjuku-ku, Tokyo
(74) Agent: Masao HORI, Patent Attorney

Carvone is constituent of essential oils

Continues on last page.

SPECIFICATION

1. Title of the Invention

Absorption Improvement Formulation

2. Scope of Patent Claims

(1) An absorption improved ubiquinone formulation comprising a dispersion of ubiquinone in an oil absorbed on a power.

(2) An absorption improved ubiquinone formulation comprising:

a dispersion of ubiquinone in an oil absorbed on a powder,

and a digestion enzyme.

3. Detailed Description of the Invention

The first and second inventions both relate to ubiquinone formulations having improved absorption. More specifically, the first invention relates to an oral ubiquinone formulation formed by absorbing on a powder a dispersion of ubiquinone in an oil. The second invention relates to an oral ubiquinone formulation having a dispersion of ubiquinone in an oil absorbed on a power, and also having a digestion enzyme.

The above described oil indicates an oil-fat, lipid, wax, refined oil, mineral oil, or mixture of such oils. This oil is a substance that is insoluble or poorly soluble in water. Most oil substances are plant oils or are liquids at room temperature like refined plant oils. However, some such oils are solids at room temperature, as exemplified by waxes, pig fat (lard), and beef fat (beef tallow).

However, this oil is preferably a liquid at room temperature from the standpoint of production of the present formulation and for absorption within the digestive tract.

The above described power can be any non-toxic powder, such as lactose powder, β-cyclodextrin, microcrystalline cellulose (AVISEL, manufactured

by Asahi Kasei Corp.), starch, wheat starch, dextrin, cellulose powder, silicon dioxide powder, or the like. More preferably, this powder has a high absorption capacity. For example, a powder can be used such as the β-dextrin granule ADSOLIDER-S (R) (manufactured by Furointo Sangyo, KK) formed using a fluid bed granulator flow coater (manufactured by Furointo Sangyo, KK) and using an α-dextrin solution as a binder.

The meaning of the term "powder" in the present invention includes fine powders and granulated powder products.

The above mentioned dispersion is taken to mean a molecular dispersion (so-called solution) or fine particulate dispersion of the ubiquinone in the oil.

Moreover, the above mentioned digestion enzyme is an enzyme that has the ability to digest food within the digestive tract, as exemplified by pepsins, trypsins, amylases, lipases, or the like. Generally digestive enzymes are classified according to the production source as animal-derived enzymes, plant-derived enzymes, or microorganism-derived enzymes.

Furthermore, a specific representative example of such a digestive enzyme is pancreatin. Pancreatin includes enzymes such as amylases, proteases, lipases, or the like.

As made clear by the below described examples, the effect of the present first invention is due to marked increase in bioavailability of ubiquinones, which are poorly soluble in water and have a large area under the curve (AUC) of concentration in the blood when taken orally. Moreover, the effect of the present second invention is a great increase in the effect of the first invention due to coexistence of the digestive enzyme with the formulation of the present first invention.

It has been previously known that dissolving a pharmaceutical in oil or dispersing the pharmaceutical in a colloidal state in oil promotes the absorption of the pharmaceutical by the digestive tract or by the skin or mucous membranes, and such preparations are marketed commercially. The inventors of the present invention discovered that a formulation formed by filling a capsule having a particle size less than or equal to 3 mm using dispersions in oil of ubiquinone and other various types of solid pharmaceuticals having poor solubility in water (such as riboflavin butyrate, ethyl amino benzoate, chloramphenicol palmitate, or the like) resulted in high bioavailability, and the inventors of the present invention discovered that this effect was further heightened by causing a digestive enzyme to be present with this formulation. Patents for such inventions were filed as Patent Application No. S55-118135 and Patent Application No. S55-146362.

As a result of further continued research thereafter, the inventors of the present invention discovered that a power formulation absorbing on a powder a dispersion of ubiquinone in an oil had bioavailability that never deteriorated despite surpassing that of a formulation that packed the above mentioned dispersion system in a capsule having a particle size less than or equal to 3 mm, and the inventors of the present invention discovered that the effect of this formulation greatly increased by having a digestive enzyme present in this formulation, thereby attaining the present invention.

Furthermore, the inventors of the present invention discovered high bioavailability for a preparation formed by dissolving ubiquinone and other various types of poorly water soluble solid pharmaceuticals in a hydrophobic organic solvent, emulsifying this solution in water in the presence of a water soluble polymeric substance, and then evaporating and removing water from the emulsion. Patents for such inventions were filed as Patent Application No. S55-70104.

In the present invention, one object of the absorption of oils on powder is to administer the formulation as is (i.e. as a powder formulation) or to administer the formulation as some sort of granule (i.e., as a fine granule, tablet, capsule, round pill, or capsule agent).

The gist of the present first invention, as mentioned previously in claim 1 of the claims, is "an absorption improved ubiquinone formulation including a dispersion of ubiquinone in an oil absorbed on a power." Moreover, the gist of the present second invention, as mentioned previously in claim 2 of the claims, is "an absorption improved ubiquinone formulation including: a dispersion of ubiquinone in an oil absorbed on a powder, and a digestion enzyme."

All ubiquinones have an isoprenoid chain. Ubiquinones are also called coenzyme Q (indicated hereinafter as CoQx), and are lipophilic (where x indicates the number of isoprenoid chains).

Ubiquinone can be blended with a liquid oil and stirred to obtain an oil dispersion system of the pharmaceutical.

The oil dispersion system of ubiquinone obtained in this manner, for example, can be absorbed on the above mentioned AVISEL (manufactured by Asahi Kasei Corp.) to obtain the pharmaceutical of the present first invention. The preferred range of the ratio of the powder to oil raw material depends on the properties of the oil and the absorptivity of the powder material.

The product is preferably finished in the form of a powder. Generally a good result is obtained if the fraction of ubiquinone in the oil dispersion system (weight basis) is less than or equal to 50 percent. The bioavailability of the formulation of the present first invention is high, and the reason for such high availability can be explained as follows.

Oils generally have high surface tension and agglomeration ability. In order to emulsify such oils in the digestive tract, the oil must be mechanically fragmented. The orally administered oil in the stomach and intestines is subjected to agitation action by the stomach and intestines and is fragmented. However, this agitation action is extremely weak in comparison to mechanical agitation. As a result, when a rather large amount of dietary oil is orally administered to a human, most of the oil is excreted without being digested. Therefore if an oil dispersion of ubiquinone is absorbed on a powder and the powder is orally administered, the oil is fragmented beforehand, surface area of the oil becomes increased, bile or lipase secretion of the patient or elderly person is low, and the oil is properly emulsified even though the agitation function of the stomach and intestines is weak. By this means, the pharmaceutical is well absorbed, and thus the bioavailability of the formulation of the present first invention is increased.

For a given amount of oil, the surface area greatly increases as the size of the droplets of the oil decreases, and the oil become more readily digested. The above described reasoning can also be readily understood from the standpoint of such ready digestion.

According to the present second invention, a digestion enzyme coexists with the dispersion, and thus the emulsification of the oil is further accelerated. It is thought as a result that a bioavailability is displayed that is at least as high as that of the first invention.

As mentioned previously, ubiquinone is lipophilic and thus is able in varying degrees to cause dispersion of oils. However, in order to sufficiently realize the effects of the present first invention and second invention, a pharmaceutical dispersion system is preferably made by selection of an oil that has as high compatibility as possible with ubiquinone.

An outline of the production methods of the present first invention and second invention will be explained next.

An oil (e.g. an edible oil) is added to ubiquinone, and the mixture is well agitated and dispersed. If a room temperature solid oil is used for the oil (e.g. lard), the oil is heated to form a liquid, the pharmaceutical powder is added to the liquid, and the mixture is agitated and dispersed.

The dispersion system prepared in this manner is next absorbed on the powder to obtain the formulation of the present first invention. In order to cause the ubiquinone dispersed in oil to absorb on the powder, the powder is preferably fed into the container of a fluidized granule coating apparatus (e.g. model FL-100, manufactured by Furointo Sangyo, KK), and the above described dispersion system is sprayed on the powder in order to obtain a uniform product. Of course, other known methods can be used for adsorbing the dispersion system on the powder. In the case of the present second invention, the digestive enzyme can be used by uniform mixing beforehand in the powder. However, the digestive enzyme can also be simply added to the formulation of the first invention. Although the oils used in the present first invention and second invention were explained previously, further specific examples are listed as follows.

Plant derived oils are exemplified by sesame seed oil, canola oil, cotton seed oil, soybean oil, camellia oil, olive oil, coconut oil, palm oil, or the like. Refined plant derived oils are exemplified by caraway seed oil, cinnamon oil, spearmint oil, peppermint oil, perilla oil, eucalyptus oil, carvone, or the like. Animal derived oils are exemplified by squalene, squalane, or the like fish oils, beef tallow, lard, mutton suet, and lipids (as exemplified by neutral fats, phospholipids, glycolipids, waxes, steroids, carotenoids, and terpenes). Mineral oils are exemplified by liquid paraffin or the like.

Examples, test results thereof and the like will be explained next. The present first invention and second invention will be explained concretely together with the results of such inventions.

Example 1

A solution containing 10 g of CoQ_{10} dissolved in 30 g of l-carvone was added to 80 g of the above mentioned ADSOLIDER-S (R) preheated to 50°C. The mixture was stirred to cause dispersion and adsorption to obtain the formulation. The above described l-carvone is a type of plant derived oil and is present in peppermint oil and spearmint oil. Ubiquinone is highly soluble in this oil.

Example 2

A solution containing 25 g of CoQ_9 dissolved in 70 g of MIGYOL 512 (manufactured by West Germany-based Dynamit Nobel AG) was added to 180 g of microcrystalline cellulose (AVISEL, manufactured by Asahi Kasei Corp.) preheated to 50°C. The mixture was stirred to cause dispersion and adsorption to obtain the formulation.

Example 3

A solution containing 35 g of CoQ_4 dissolved in 35 g of squalene was added to 180 g of powdered lactose. The mixture was stirred to cause dispersion and adsorption to obtain the formulation.

Example 4

Lipase AP6 manufactured by Amano Enzyme Inc. was granulated using a centrifugal fluidized granule coating apparatus manufactured by Furointo Sangyo, KK to form granules in the 1 to 0.5 mm particle size range, and the same equipment was further used to apply an enteric coating and produce enteric lipase AP6 pills. These enteric lipase AP6 pills (60,000 to 65,000 units as lipase AP6, 25 g as lipase AP6) were added to 60 g of the ubiquinone formulation of Example 1. The mixture was dispersed and mixed to obtain the formulation.

Example 5

PROZYME 6 manufactured by Amano Enzyme Inc. was granulated using a centrifugal fluidized granule coating apparatus manufactured by Furointo Sangyo, KK to form granules in the 1 to 0.5 mm particle size range, and the same equipment was further used to apply an enteric coating and produce enteric PROZYME 6 pills. These enteric PROZYME 6 pills (60,000 to 65,000 units, 30 g as PROZYME 6) were added to 110 g of the ubiquinone formulation of Example 2. The mixture was dispersed and mixed to obtain the formulation.

The ubiquinone formulations of the above various examples were administered orally to beagle dogs at a dose of 100 mg/ body as ubiquinone. The concentration of ubiquinone in blood (μg/mL) for each beagle dog is shown Table 1 and FIG. 1. Ubiquinone raw powder was used as a control for each of these tests.

Table 1
(concentration in blood, μg/mL)

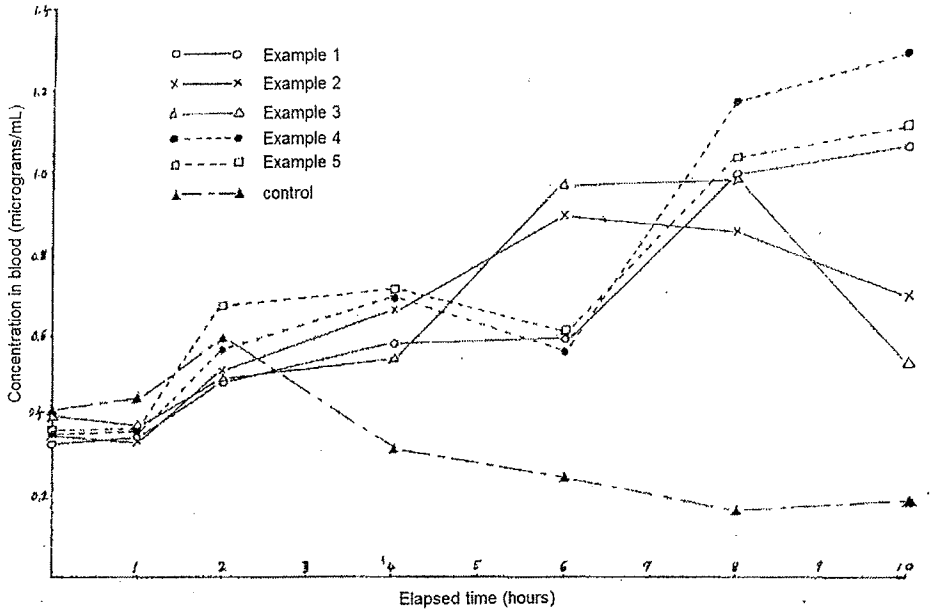
Elapsed time / Formulation	0	1	2	4	6	8	10
Example 1	0.33	0.35	0.49	0.59	0.60	1.01	1.08
Example 2	0.35	0.34	0.52	0.67	0.91	0.87	0.71
Example 3	0.40	0.38	0.50	0.55	0.99	1.00	0.54
Example 4	0.35	0.36	0.57	0.70	0.57	1.19	1.31
Example 5	0.36	0.36	0.68	0.72	0.61	1.05	1.13
control	0.41	0.45	0.60	0.32	0.25	0.17	0.19

4. Brief Description of the Drawings

FIG. 1 is a graph of test results of the concentration in blood using beagle dogs and the ubiquinone formulations of each of the above described examples. The vertical axis indicates the concentration of ubiquinone in blood. The horizontal axis indicates the elapsed time.

Agent: Masao HORI, Patent Attorney

FIG. 1



Continued from Page 1

(72) Inventor: Emiko SUDO
c/o Furointo Sangyo, KK
14-2 Takadanobaba 2-chome
Shinjuku-ku, Tokyo-to

(72) Inventor: Takuichi TSUJINO
c/o Furointo Sangyo, KK
14-2 Takadanobaba 2-chome
Shinjuku-ku, Tokyo-to

Amendment of Proceedings (self originating)

April 20th, 1981
[*content of stamp: illegible*]

The Hon. Commissioner of the Patent Office:

1. Case Identification
   Patent Application No. S56-27663
2. Title of the Invention: Absorption Improvement Formulation
3. Person Filing Amending
   Relationship to the Case: Patent Applicant
   Furointo Sangyo, KK
   14-2 Takadanobaba 2-chome
   Shinjuku-ku, Tokyo-to
4. Agent
   Attorney (7353) Masao HORI [*seal of Attorney HORI*]
   5-9-11 Chuo
   Nakano-ku, Tokyo-to, postal code 164
   Phone no.: 03-381-0496
5. Subject of Amendment
   "Detailed Description of the Invention" of the Specification
6. Content of the Amendments
   (1) Line 5 of page 4 of the Specification:
   Correct "having a large ... (AUC) and poorly soluble in water ..." to read
   "having a large ... (AUC), well absorbed by lymph vessels, and poorly soluble in water ..."
   (2) Lines 9 and 10 of page 4 of the Specification:
   Correct "... in that ... is greatly increased" to read
   "... in that ... is greatly increased. Furthermore, absorption by the lymph vessels is thought to occur due to transfer to the lymph vessels from the digestive tract. Transfer of the pharmaceutical to the lymph vessels is advantageous since a pharmaceutical transferred to the lymph vessels differs from the pharmaceutical transferred to the blood in that the pharmaceutical in the lymph vessels is not sent by the portal vein to the liver and is not metabolized in the liver."
   (3) Line 5 of page 8 of the Specification:
   Correct "the pharmaceutical is well absorbed ..." to read
   "the pharmaceutical is well absorbed from the digestive tract by the blood and the lymph vessels."